"MATERNAL FOLATE STATUS AND PLACENTAL NEURO VASCULAR CHANGES IN PREGNANT WOMEN WITH EARLY ONSET PREECLAMPSIA VERSUS LATE ONSET PREECLAMPSIA"

Synopsis

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Abstract

Background: Preeclampsia is a hypertensive disorder of pregnancy, affects both maternal and fetal health. The study aims to assess maternal folate status and placental neurovascular changes in pregnant women with early-onset preeclampsia (EOPE) compared to those with late-onset preeclampsia (LOPE). The research is based on the hypothesis that impaired one-carbon metabolism, evidenced by low folate and high homocysteine, may initiate a cascade of events leading to the clinical manifestations of preeclampsia. The study also seeks to evaluate pregnancy outcomes and the correlation between various biomarkers and these outcomes. **The objective of the study is i. to** assess the maternal folate status and placental expression of neurovascular markers in late-onset preeclampsia when compared to early-onset preeclampsia. **ii.** To Assess the pregnancy Outcome among the groups**. iii.** To assess the correlation between the biomarkers and pregnancy Outcome

Methodology: This was a case-control, observational study conducted at the OBG department of MGMCRI. Briefly 135 blood samples were collected from each group (n=45) such as_Group I: healthy pregnant control women, **Group II:** women with early-onset preeclampsia, Group III: 45 women with late-onset preeclampsia. Also placental samples were collected from every 4th subject for a total of 10 samples per group. The study assessed various parameters, including maternal folate status, blood biochemical markers and circulatory neurovascular markers. Pregnancy outcomes were recorded.

Results: The findings showed significant clinical differences between the groups, particularly in blood pressure, gestational age at delivery, and birth weight. The early-onset preeclampsia group had the lowest gestational age at delivery and birth weight, Regarding biomarkers, both preeclampsia groups showed significantly lower serum folate and serum tetrahydrofolate levels and elevated homocysteine levels compared to the control group. The Early Onset Preeclampsia group had significantly higher levels of uric acid, urea, and creatinine, as well as liver enzymes AST and ALT, compared to the other groups, Dysregulated lipid profiles were also noted in both preeclampsia groups.

Conclusion: The study's results support the proposed mechanism that maternal folate deficiency may initiate a cascade of events leading to the clinical manifestations of preeclampsia. This pathway involves dysregulated lipid metabolism, hepatic and renal stress, and systemic inflammation and neuronal injury, which ultimately contribute to adverse pregnancy outcomes such as premature birth and low birth weight. The findings highlight the distinct metabolic and physiological profiles of early-onset preeclampsia, suggesting that the underlying path physiology is more severe than in late-onset case

1. INTRODUCTION

Pre-eclampsia is one of the most severe hypertensive disorder, where (blood pressure ≥140/90 mmHg on at least 2 occasions in 4-6 hrs apart) during pregnancy after 20 wks of gestation[3] with/ without proteinuria disorders of pregnancy. Pre –eclampsia threatens 4 - 5% of gravidas in the world wide and is a leading cause of maternal and neonatal morbidity and mortality.[1,2]

From the past two decades, various mechanisms have been proposed for causing pre-eclampsia, including defective placentation, imbalance in circulating angiogenic factors, placental ischaemia and hypoxia, abnormal immune interaction at the maternal-foetal interface though none have conclusive evidence in humans.[4]

Preeclampsia is further classified as "Early preeclampsia" if it occurs <34 weeks of gestation and "late preeclampsia" ≥ 34 weeks of gestation based on the timing of clinical symptoms present[5] this classification is based on ACOG guidelines 2016.

Folate is critical for normal fetal development and growth and maternal folate deficiency is associated with poor pregnancy outcomes. [6,7] . Untreated preeclampsia, regardless of the phenotype, can result in severe complications including liver rupture, cerebral hemorrhage, myocardial infarction, stroke, acute respiratory distress syndrome, pulmonary edema, kidney failure, and abruptio placentae[9].

Homocysteine is a metabolite of folate. It is an independent risk factor for cardiovascular disease [10]. About 20–30% of patients with coronary artery and peripheral vascular disease develop with hyperhomocysteinemia [11]. When the level of homocysteine is increased, it is easily oxidized to form homocysteine compounds, and at the same time, hydrogen peroxide and superoxide ion radicals are generated, which damages vascular endothelial cells and causes a series of vascular damage [12]. S100B and Neuro peptide is used as Neurovascular markers to evaluate the Neural changes occurred in Early onset Preeclampsia Versues Late Onset Preeclampsia.

On processing of neurovascular markers and Blood biomarkers the overall results summarizes that early onset preeclampsia involves more severe patho-physiology than late onset preeclampsia.

2. AIMS AND OBJECTIVES

2.a. AIM:

To find the association between maternal folate status and Placental Neuro-vascular changes in pregnant women with early onset preeclampsia compared to late onset preeclampsia.

2.b. OBJECTIVES :

- **PRIMARY OBJECTIVES**

– To evaluate the maternal folate status of neurovascular markers in early onset preeclampsia when compared to late onset preeclampsia.

- **SECONDARY OBJECTIVES**

– To assess the pregnancy outcome among preeclampsia when compared to healthy pregnant women.

– To assess the correlation between the biomarkers and the pregnancy outcomes.

2.c : STUDY TYPE:

Cross Sectional Observational Study.

3. REVIEW OF LITREATURE

Pre-eclampsia is a leading complication of pregnancy that affects an estimated 4–5% of pregnancies worldwide .[3]This disease incurs a large burden of maternal and fetal morbidity and mortality, with substantial contributions to prematurity of the fetus and long-term cardiovascular disease (CVD) in the mother . Pre-eclampsia is defined as the presence of new-onset hypertension and proteinuria or other end-organ damage occurring after 20 weeks gestation, whereas eclampsia is defined as the development of grand mal seizures in a woman with pre-eclampsia.

Folic acid (FA), also known as pteroyl glutamic acid, is a water-soluble B vitamin which exists in the form of FH4 in human body [8]. It is involved in protein and fat metabolism and fetal neural tube cell division and growth [12]. FA is an important coenzyme of cell DNA synthesis and plays an important role in placental production and fetal growth and development [13]. A sufficient amount of FA could reduce the incidence of megaloblastic anemia and abortion, promote fetal growth and development, expand placental blood vessels, and increase placental blood supply [14]. There is emerging evidence that supplementation with high doses of or long-term use of FA could effectively prevent pre-eclampsia [15]. In contrast, recent study conducted on mice shows that mice fed with 5-fold higher folic acid than recommended for mice (5xFASD) during pregnancy, resulted in methylenetetrahydrofolate reductase (MTHFR) deficiency. It has also been found that the diet with 5xFASD resulted in alterations in placental expression of 29 genes involved in angiogenesis, receptor biology, neurodevelopment and DNA methylation [9]. This gives a clue about the DNA methylation changes and the possible pathogenic

changes related to folate metabolism.

Homocysteine is a metabolite of folate. Homocysteine is an independent risk factor for cardiovascular disease [10]. About 20–30% of patients with coronary artery and peripheral vascular disease develop hyperhomocysteinemia [11]. When the level of homocysteine is increased, it is easily oxidized to form homocysteine compounds, and at the same time, hydrogen peroxide and superoxide ion radicals are generated, which damages vascular endothelial cells and causes a series of vascular damage [12]. It has been reported that homocysteine is one of the causes of the onset of hypertensive disorders in pregnancy [16]. Recent studies show that a decreased plasma folate and elevated plasma homocysteine are associated with incidence of preeclampsia, low birthweight and preterm birth[17,18].

Preeclampsia may further be classified based on the onset of preeclampsia and late onset preeclampsia based on the onset of hypertension and or proteinuria before or after 34 weeks of gestation respectively. It is believed that early onset preeclampsia may have poor prognosis when compared to late onset preeclampsia(5). In our study, we are trying to make an attempt to assess the maternal folate status in the blood and associate with the placental neurovascular markers among early onset preeclampsia versus late onset preeclampsia.

4. RESEARCH QUESTION OR HYPOTHESIS

Is the maternal folate levels associated with placental neuro-vascular changes in pregnant women with early onset preeclampsia versus late onset preeclampsia.

5. STUDY SUBJECT AND METHODOLOGY

5.a. Mode of selection of Study subjects:

All the study participants will be pregnant women of age group 18-35 years, who are admitted the Department of Obstetrics and Gynecology, MGMCRI hospital for delivery. After obtaining an informed consent from the study subjects, venous blood will be collected during the third trimester between 30- 38 weeks of gestation ante-partum just before the delivery or induction. Placental samples will be collected immediately after delivery. The study subjects will be classified into 3 groups as follows (Groups I, II and III),

i. Number of groups to be studied: 3 groups

Group I: Pregnant Control women

Group II: Preeclampsia (early onset)

Group III: Preeclampsia (late onset)

ii. Sample size calculation:

A total of 135 study subjects will be selected comprising 45 study subjects in each group.

Sample size determination:

SAMPLE SIZE CALCULATION FOR STUDY I

For the sample size calculation of study I, The sample size was calculated using mean and standard deviations of various parameter such as s100b, sVEGFR1, PLGF etc and it has been found that s100 b had the most number of sample size predicted for the assay. The sample size was calculated using the mean and SD values of s100b obtained from preeclampsia group as 0.07 ± 0.05 and control groups as 0.04 ± 0.05 from vetorrazzi et al 2012 (20) and sample size obtained is 44 per group which is rounded off as 45. Since there are 3 groups, the total sample size was calculated to be 135. The calculation was done using the Open Epi open source epidemiologic statistics for public health, version 3.01 using the power as 80, and ratio of sample size as 1, confidence interval as 95%.

SAMPLE SIZE CALCULATION FOR STUDY II.

Similarly the sample size for placental samples were calculated using mean and standard deviations of VEGF expressions in preeclampsia as 1.8 ± 0.4 and control group as 3.85 ± 0.6 as shown in fig 1 and 2 from Fanzhen et al 2014 (21) and sample size obtained is 2 per group. In order to achieve better significance, the sample size was fixed at 10 per groups. Since there are 3 groups, the total sample size was calculated to be 30. The calculation was done using the Open Epi open source epidemiologic statistics for public health, version 3.01 using the power as 90, and ratio of sample size as 1, confidence interval as 95%. The placental samples will be collected from every 3rd samples of the study subjects recruited for the evaluation of biochemical markers.

5.b Sample size determination:

Calculation: Serum s100B, 0.07 ± .05 in Preeclampsia vs 0.04 ± 0.05 in healthy controls

Reference: vettorazzi et al

Software: Open epi. Ver 3.1

5.c Inclusion and exclusion criteria:

The following inclusion and exclusion criteria will be followed in the study.

Inclusion criteria: Pregnant women with age between 18-35 years.

Inclusion criteria specific to the different groups of the study.

Groups	Inclusion criteria
Group I: Control Pregnant women	Healthy pregnant women with age 18- 30 years, who do not have present or past history of hypertensive disorders and any of the complications of pregnancy.
Group II: Early onset Preeclampsia	Onset of hypertension and proteinuria between 20wks and 34 wks of gestation in previously normotensive non proteinuric pregnant women . (Presence of proteinuria of 2+ or more on dipstick analysis
Group III: Late onset Preeclampsia	Onset of hypertension and proteinuria after 34 wks of gestation in previously normotensive non proteinuric pregnant women with age . (Presence of proteinuria of 2+ or more on dipstick analysis)

Exclusion Criteria: Pregnant women with major congenital anomalies, kidney disease, autoimmune disorders and infections in current pregnancy will be excluded from the study.

5.d STUDY PARAMETERS:

a. Demographic details
    - Anthropometric measurement (Age, BMI (at first antenatal visit), Gravida, History of previous pregnancy.

b. Blood Biomarkers
    - Serum Tetra hydrofolate, homocysteine and vitamin B12- ELISA
    - Neurovascular markers such as -Neuropeptin, s100b by ELISA

c. Placental expressions
    - Neuropeptin, s100b, Placental folate Transporter and Neurovascular marker by gene expression

d. Pregnancy outcome:
    - Gestational age (GA) at the time of delivery
    - Birth weight of the baby
    - APGAR Score

6. RESULTS

Results on analysis of various parameters in different method shows the following results:

Table 1 : The data of Table 1 suggests that **Early-Onset Preeclampsia (EOPE)** is a more aggressive form of the condition. It results in earlier delivery, lower birth weight, and lower neonatal vitality scores compared to Late-Onset Preeclampsia. While LOPE still presents hypertensive risks, the fetal outcomes are significantly closer to those of the healthy Control group.

Table 2: The Tale 2 indicates that the both forms of preeclampsia pose significant risk, **Early-Onset Preeclampsia (EOPE)** is associated with a much higher burden of neonatal morbidity and more profound biochemical derangement. These findings emphasize the importance of early screening (specifically using **sFlt-1/PLGF ratios** and **Homocysteine** levels) to identify high-risk pregnancies and manage delivery timing to optimize both maternal and neonatal survival.

Table 3a : T he data of the Table 3 demonstrates that **Early-Onset Preeclampsia (EOPE)** and **Late-Onset Preeclampsia (LOPE)** are distinct in their severity and biochemical profiles.

- **EOPE** is characterized by severe hypertension, significantly earlier delivery, and poorer neonatal outcomes (low birth weight and APGAR scores).
- **Biochemical Signature:** Preeclampsia is strongly associated with an angiogenic imbalance (high sFlt-1/low PLGF), hyperhomocysteinemia, and depleted folate levels.
- **Statistical Significance:** The differences in Homocysteine, Hemoglobin, Serum Iron, and Ferritin between the Control and both preeclampsia groups are all statistically significant ($p < 0.05$), highlighting these as critical markers for the condition.
- Significant differences in neuro-inflammatory markers (IL-6, S100B) , suggest that preeclampsia's impact extends beyond the vascular system into systemic inflammation and potential neurological stress. The more extreme deviations in nearly all measured parameters for the EOPE group suggest a more profound placental failure and systemic response than those found in LOPE.

Ultimately, the more extreme biochemical derangements in the EOPE group suggest a more profound failure of placental development compared to LOPE, necessitating earlier medical intervention to manage maternal and fetal risks.

- **Table 3b:** The Table 3c indicates the Elevation of neuro-inflammatory markers (IL-6, S100B, Synapsin 1) suggest that preeclampsia triggers a broad systemic response affecting both maternal inflammatory status and potentially neurological health.
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- **Table 4;**: The data of table 4 collectively demonstrates the Early-Onset Preeclampsia (EOPE) represents a significantly more severe clinical and biochemical phenotype than Late-Onset Preeclampsia (LOPE). EOPE is characterized by severe hypertension, earlier diagnosis/delivery, and poorer neonatal outcomes. Across both types, the disease is marked by a "molecular signature" of folate depletion, elevated homocysteine, iron overload, and a profound angiogenic imbalance, all of which contribute to the systemic inflammatory and vascular damage seen in preeclampsia.

Morphological changes in Placenta of Preeclampsia :

 EOPE is Clinically Superior in Severity: While both forms are dangerous, Early-Onset Preeclampsia (EOPE) presents a more profound failure of placental development. This is evidenced by the most extreme deviations in blood pressure, birthweight, and angiogenic markers (sFlt-1/PLGF).

 Structural Failure Drives Clinical Symptoms: The histopathological findings of endarteritis obliterans and syncytial knots confirm that the clinical symptoms (hypertension) and fetal outcomes (low birthweight) are directly caused by physical obstructions in placental blood vessels.

 Biochemical Predictors: Depleted folate and elevated homocysteine, combined with angiogenic imbalance, serve as critical systemic markers for the disease. In particular, Uric Acid was identified as a significant predictor specifically within the EOPE group.

Placental m- rna Expression of Vascular Endothelial growth factor in EOPE vs LOPE

The Placental m-RNA Expression of VEGF shows that **Early-Onset Preeclampsia (EP)** is a distinct clinical entity with a much higher biological impact than Late-Onset Preeclampsia (LP). While LP outcomes often mirror healthy pregnancies, EP cases show a doubling of this specific stress marker, correlating with the higher blood pressure (161.51 mmHg) and lower birth weights (1.87 kg) documented in the clinical tables.

The overall expression indicates that EOPE is more dangerous than LOPE as there will be more stressed in placenta and also low birth weight, lower the birth age and also all the above parameters shows the statistically significant in EOPE.

Table 1. Clinical and Pregnancy Characteristics Sample Size :

Parameter	Control	EOPE	LOPE
Age (years)	27.51 ± 3.28	27.82 ± 2.78	28.80 ± 2.43
BMI (kg/m²)	22.64 ± 2.89	23.76 ± 3.19	23.40 ± 2.64
Systolic BP (mmHg)	112.83 ± 8.03	161.51 ± 11.92	150.97 ± 9.49
Diastolic BP (mmHg)	71.68 ± 6.03	99.04 ± 9.32	99.25 ± 9.09
Gestational age at diagnosis (weeks)	NA	31.19 ± 1.42	35.82 ± 0.88
Gestational age at delivery (weeks)	39.25 ± 0.98	33.29 ± 1.77	37.89 ± 1.42
Birthweight (kg)	3.03 ± 0.29	1.87 ± 0.39	2.65 ± 0.42
Apgar score at 1 min	8.60 ± 0.65	7.27 ± 1.01	8.16 ± 0.85
Apgar score at 5 min	9.36 ± 0.57	8.44 ± 0.81	8.89 ± 0.68

Control n= 45, EOPE n= 45, LOPE n=45 Note: Values are presented as **Mean ± Standard Deviation (SD)**. Comparisons between groups (Control, EOPE, LOPE) were performed using **one-way ANOVA**, with ***p < 0.05** considered statistically significant. Clinical characteristics such as age, BMI, and blood pressure were recorded at recruitment. Gestational age was determined from the last menstrual period and/or early ultrasound. Birthweight and Apgar scores were recorded at delivery. Abbreviations: BMI – Body Mass Index; BP – Blood Pressure; EOPE – Early-onset preeclampsia; LOPE – Late-onset preeclampsia

Table 2. Folate–Homocysteine and Iron Status:

Parameter	Control	EOPE	LOPE
Serum folate (ng/mL)	12.18 ± 2.76	8.60 ± 2.71*	9.55 ± 2.28*
Serum Tetrahydrofolate (ng/mL)	11.69 ± 2.53	9.14 ± 2.60*	9.74 ± 2.49*
Homocysteine (µmol/L)	8.91 ± 1.50	13.04 ± 2.13*	11.69 ± 2.09*
Hemoglobin (g/dL)	11.00 ± 0.64	9.85 ± 3.01	10.38 ± 2.02

Serum Iron (µg/dL)	78.14 ± 11.21	85.18 ± 11.34*	87.62 ± 12.04*
Ferritin (ng/mL)	36.56 ± 7.85	41.51 ± 8.24*	58.96 ± 8.94*
Sflt-1 (pg/ml)	4.5 ± 1.57	7.25 ± 1.08*	6.87 ± 1.46 *
PLGF (ng/ml)	233.32 ± 149.92	45.28 ± 34.78 *	61.1 ± 51.39 *#

Note: Values are presented as Mean ± SD. N=45/grp. Group comparisons were analyzed using one-way ANOVA with post hoc tukey, with *p < 0.05 considered significant. Dietary folate intake was estimated from validated food frequency questionnaires, while serum folate and tetrahydrofolate were measured using immunoassays. Homocysteine levels were assessed by enzymatic assays, and iron indices (hemoglobin, serum iron, ferritin) were determined using standard biochemical methods. Abbreviations: EOPE – Early-onset preeclampsia; LOPE – Late-onset preeclampsia; SD – Standard Deviation.

Table 3 a :Inflammatory, Neuronal and Angiogenic Markers

Comparision Between	**Homocysteine (µmol/L)**		**Haemoglobin(g/dl)**		**Serum Iron (µg/ml)**		**Ferritin (ng/ml)**	
	Difference	**P value**	**Difference**	**P value**	**Difference**	**P value**	**Difference**	**P value**
Control & EOPE	**4.13**	**<0.0001 (S)**	**1.16**	**<0.0001 (S)**	**16.96**	**<0.0001 (S)**	**15.05**	**<0.0001 (S)**
Control & LOPE	**2.78**	**<0.0001 (S)**	**0.62**	**0.0041(S)**	**9.52**	**0.0005 (S)**	**7.59**	**<0.0001 (S)**
EOPE & LOPE	**1.35**	**0.0034(S)**	**0.53**	**0.0168(S)**	**7.44**	**0.0086 (S)**	**7.45**	**<0.0001 (S)**

Table 3 b :Inflammatory, Neuronal and Angiogenic Markers

Comparison Between	**sVEGFR1 (pg/ml)**		**Placental Growth factor (pg/ml)**		**Neuropeptin (pg/ml)**		**S 100 B (ng/ml)**		**Synapsin1 (ng/ml)**	
	Difference	**P value**	**Difference**	**P value**	**Difference**	**P value**	**Difference**	**P value**	**Difference**	**P value**
Control & EOPE	**12600.56**	**<o.ooo1 (S)**	**336.82**	**<o.ooo1(S)**	**45.53**	**<0.0001(s)**	**0.07**	**<0.0001 (s)**	**0.56**	**<0.0001(s)**

Control & LOPE	**6699.57**	**<o.ooo1 (S)**	**251.57**	**<o.ooo 1(S)**	**26.32**	**0.0002 (s)**	**0.04**	**<0.0001 (s)**	**0.26**	**0.045 9**
EOPE & LOPE	**5900.99**	**<o.ooo1 (S)**	**85.25**	**<o.ooo 1(S)**	**19.21**	**0.0099 (s)**	**0.03**	**<0.0001(s)**	**0.29**	**0.021 1(s)**

Table 4. Multiple regression analysis predicting Neuropeptin (pg/mL) in Control, EOPE, and LOPE groups

Group	Significant Predictors	Coefficient	p-value	R^2	F-value	Residual Std. Error	AIC
Control	**Age (Years)**	**-2.95**	**0.088***	**0.735**	**1.58**	**22.74**	**423.89**
	BMI (kg/m²)	**-4.28**	**0.022****	**-**	**-**	**-**	**-**
	Systolic BP (mmHg)	**1.56**	**0.043****	**-**	**-**	**-**	**-**
	Serum Tetrahydro folate (ng/mL)	**6.35**	**0.034****	**-**	**-**	**-**	**-**
	Glucose (mg/dL)	**-1.58**	**0.034****	**-**	**-**	**-**	**-**
EOPE	**Uric Acid (mg/dL)**	**12.49**	**0.093***	**0.699**	**1.19**	**32.28**	**452.95**
LOPE	**None**	**—**	**—**	**0.491**	**0.49**	**37.50**	

Note: *p < 0.1 indicates a trend toward significance, and *$p < 0.05$ indicates statistical significance. Only significant or near-significant predictors are presented in the table; non-significant variables are omitted for clarity. Model fit statistics, including R^2, F-value, Residual Standard Error, and AIC, are shown for each group.

7. DISCUSSION

The findings showed significant clinical differences between the groups, particularly in blood pressure, gestational age at delivery, and birth weight. The early-onset preeclampsia group had the lowest gestational age at delivery and birth weight, Regarding biomarkers, both preeclampsia groups showed significantly lower serum folate and serum tetrahydrofolate levels and elevated homocysteine levels compared to the control group. The Early Onset Preeclampsia group had significantly higher

levels of uric acid, urea, and creatinine, as well as liver enzymes AST and ALT, compared to the other groups, Dysregulated lipid profiles were also noted in both preeclampsia groups.

8. CONCLUSION

The study's results support the proposed mechanism that maternal folate deficiency may initiate a cascade of events leading to the clinical manifestations of preeclampsia. This pathway involves dysregulated lipid metabolism, hepatic and renal stress, and systemic inflammation and neuronal injury, which ultimately contribute to adverse pregnancy outcomes such as premature birth and low birth weight. The findings highlight the distinct metabolic and physiological profiles of early-onset preeclampsia, suggesting that the underlying path physiology is more severe than in late-onset cases.

9. LIMITATIONS

The Limitation of the above study is as the patient cannot be followed up from the first trimester.

10. FUTURE ASPECTS

Untreated preeclampsia leads to eclampsia where it is more dangerous and life threaten disease. As per our study by using the neurovascular marker preeclmapisa can be detected at the earliest and treated accordingly.

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MEMBER SECRETARY
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Associate Professor
Dept. of Pharmacology,
MGMCRI, Puducherry.
Email: ihec@mgmcri.ac.in

CERTIFICATE OF APPROVAL

Project No: MGMCRI/2024/RAC/02/IHEC/11 **Date:** 26/02/2024

Project Title:

MATERNAL FOLATE STATUS AND PLACENTAL NEURO-VASCULAR CHANGES IN PREGNANT WOMEN WITH EARLY ONSET PREECLAMPSIA VERSUS LATE ONSET PREECLAMPSIA".

Study period: This approval is valid for the **one year** duration of the study and shall be considered for extension by IHEC, upon request with in sufficient time by the PI.

Principal Investigator: Mrs. RASHMI RN

Type of review:
Full Board Review

Date of review (D/M/Y): 01/02/2024

Date of previous review, if revised application:

- ✓ It is understood that the study will be conducted under your direction, in a total of ***135*** research participants, at as per the submitted protocol.
- ✓ **The IHEC approves the above mentioned study**
- ✓ For studies which will continue for more than a year, a continuing review report needs to be submitted (within1 month of the due date i.e. 11 months from the date of approval) on or before **26/01/2025**

26/02/24.

Dr. BARATHANE D
MEMBER SECRETARY
Institutional Human Ethics Committee
MGMCRI, Puducherry - 607 402

Office of Institutional Human Ethics Committee, College Block, 1st floor, (Adjacent to Dept of Pathology
MGMCRI, Puducherry – Cuddalore Main Road, Pillayarkuppam, Puducherry 607 403, INDIA
Email: ihec@mgmcri.ac.in, Telephone No: 0413 -2616700 (Extension No: 754)

PRE PHD EXAM Certificate

SRI BALAJI VIDYAPEETH
Examinations

OFFICE OF THE CONTROLLER OF EXAMINATIONS
Dr. **S. SRIRANGARAJ**
Controller of Examinations

Date: 21-06-2023

No. SBV/COE/Ph.D/A5

UNIVERSITY MEMORANDUM

Sub : Sri Balaji Vidyapeeth – Ph.D Degree in Part – I Course Work Assessment – Results Notified.

* * * * *

Mr/Mrs/Dr. **RASHMI R N**, UIN. **2105002029** Research Scholar in Medicine (Part Time - External) is declared to have passed the Ph.D Part-I – Course Work Assessment and he/she is permitted to continue the research under the guidance of Dr. **VICKNESHWARAN V** and submit the thesis for the award of Ph.D Degree as per the regulations of SBV.

Sl. No.	Subjects	Result Status
1	PAPER - I RESEARCH METHODOLOGY AND BIOSTATISTICS	**PASS**
2	PAPER - II ON CHOSEN FIELD OF RESEARCH	**PASS**

SRI BALAJI VIDYAPEETH CONTROLLER OF EXAMINATIONS PONDICHERRY

S. Sriranga raj
CONTROLLER OF EXAMINATIONS

To : Mr/Mrs/Dr. **RASHMI R N**

CC : Dr. **VICKNESHWARAN V**, Asst. Prof. of Biochemistry, MGMCRI.

Publications

Journal of Chemical Health Risks
www.jchr.org
JCHR (2025) 15(2), 294-299 | ISSN:2251-6727

The Potential Role of Folic Acid in Preventing and Managing Preeclampsia: A Systematic Review

Rashmi R Naganna[1,2], Vickneshwaran Vinayagam[1*], Seethesh Ghose[3]

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(Received: 16 January 2025 Revised: 20 February 2025 Accepted: 20 March 2025)

KEYWORDS

Preeclampsia, folic acid, homocysteine

ABSTRACT:

Preeclampsia, a life-threatening pregnancy complication, affects both maternal and fetal health. Folic acid, a crucial B-vitamin, plays a vital role in preventing birth defects and promoting healthy pregnancy outcomes. This review aims to explore the relationship between folic acid and preeclampsia, highlighting its mechanisms of action and potential therapeutic benefits. Folic acid's impact on endothelial function, homocysteine metabolism, antioxidant activity, and methylation processes, and placental development may prevent preeclampsia risk. Observational studies suggest that higher folic acid intake is associated with a reduced risk of preeclampsia, while randomized controlled trials demonstrate a trend towards a protective effect. However, results are not consistently replicated across different populations. Healthcare providers should consider individualized folic acid supplementation recommendations, taking into account medical history, dietary habits, and risk factors for preeclampsia. A balanced diet rich in folate-containing foods, combined with other essential vitamins and minerals, is essential for optimal outcomes. Future research directions include personalized approaches based on genetics and risk factors, exploring combined interventions, and investigating the impact of folic acid on DNA methylation and gene expression. Developing early biomarkers for preeclampsia risk could help identify women who could benefit from targeted interventions. In conclusion, folic acid plays a critical role in preventing preeclampsia by influencing various cellular processes. While its effects may vary based on individual health conditions and genetic factors, folic acid supplementation holds promise for improving maternal and fetal health outcomes.

1. Introduction to Preeclampsia and Folic Acid

Pregnancy is a transformative and crucial period in a woman's life, marked by various physical and physiological changes. However, it can also bring about certain complications that require careful attention and management. Preeclampsia is a pregnancy complication that affects pregnant women, and an important factor in ensuring a healthy pregnancy is the intake of essential nutrients like folic acid.(1) Preeclampsia is a complex disorder that typically occurs after the 20th week of pregnancy and is characterized by high blood pressure and damage to organs such as liver and kidneys. This condition can lead to serious complications for both the mother and fetus. While the exact cause of preeclampsia is not fully understood, it's believed to be related to issues with the placenta, the organ that connects the developing fetus to the uterine wall. Preeclampsia often presents with symptoms such as high blood pressure, protein in the urine (a sign of kidney problems), swelling of the hands and face, severe headaches, and changes in vision. Left untreated, it can escalate into a more severe condition called Eclampsia, which involves seizures and can be life-threatening for both the mother and the baby. Early detection and proper prenatal care are essential in managing and minimizing the risks associated with preeclampsia. (2)

2. Methods

The databases available on the online web sources such as Google Scholar, Pubmed, Research gate and Biomed

ZHUZAO/FOUNDRY

ISSN NO:1001-4977

Ugc Care Approved Group II Journal

Manuscript Acceptance Letter

Date : 19-11-2025

Dear Author,

Congratulations! As a result of reviewers and revisions, we are pleased to inform that your following manuscript has been formally accepted for publication in Foundry journal.

Tittle: Assessment of Neuromarkers in Early-Onset Versus Late-Onset Preeclampsia: A Comparative Analysis Using Serum Biomarkers and Clinical Indicators.

Manuscript Id: FJ25/C916

Volume 28 Issue 11 (NOVEMBER Edition 2025)

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Scope

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Subject: Paper Number 280416 Accepted for Publication in SCOPE

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To

Vickneshwaran Vinayagam

Dear researcher

We hope you are in good health. We are pleased to inform you that your paper has been **accepted for publication** in *Journal SCOPE*. Kindly complete the payment of the **publication fee** through our official webpage **by 05 January 2026**. After completing the transaction, please **email us the payment confirmation** along with the **deposit proof** for our records. Should you have any questions or require assistance, please do not hesitate to contact us. We appreciate your contribution to *Journal SCOPE* and look forward to publishing your valuable research.

Paper No.	Paper Title	Status
280416	Development and Validation of a Food Frequency Questionnaire to Assess Dietary Iron and Folate Intake among Pregnant Women in a South Indian Population	Accepted

Warm Regard
Van Heerde
Executive Editor
29.12.2025

We Indexed in Cosmos, Baidu Scholar, Dimensions, Google Scholar, Publons, Scopus, Scimago, Semantic Scholar

RPE & RMBS Exam Certificate

PERFORMANCE ASSESSMENT OF Ph.D. STUDENTS OF 2020 & 2021 BATCHES IN RESEARCH METHODOLOGY & BIOSTATISTICS (RMBS) AND RESEARCH PUBLICATION ETHICS (RPE)(Part I- Paper 1) COURSES CONDUCTED ONLINE BY DEANERY RESEARCH, SBV

To:

SBV Ph.D. Scholars Batches 2020 AND 2021and their respective Guides

9.	2105002029	RASHMI R N	Dr. VICKNESHWARAN V, Assistant Professor, Department of Biochemistry, MGMCRI	**Successfully participated and passed**	24.08.2022

SRI BALAJI VIDYAPEETH

ACCREDITED BY NAAC WITH 'A++' GRADE
LISTED U/S 12B OF THE UGC ACT, 1956

DEEMED TO BE UNIVERSITY
DECLARED U/S 3 OF THE UGC ACT, 1956

CREDIT POINT 4

CERTIFICATE

This is to Certify that Dr./Mr./Ms..... Rashmi R N .....

UIN No..... 2105002029 .....*Department of .....* Biochemistry .....

has attended, actively participated and fulfilled the requirements as per University norms of the online workshop on ***"RESEARCH METHODOLOGY, BIO-STATISTICS AND PREPARATION OF SCIENTIFIC MANUSCRIPT"*** *conducted by Sri Balaji Vidyapeeth, Puducherry from 18.05.2022 to 24.06.2022*

Dr.G.Ezhumalai
Course Coordinator

Dr. S.R. Rao
Vice President (R,I & D)

Dr.Subash Chandra Parija
Vice Chancellor

ORAL AND POSTER PRESENTATIONS

அண்ணாமலைப் பல்கலைக்கழகம்
Annamalai University
ACCREDITED WITH A+ GRADE BY NAAC

emsi
ENVIRONMENTAL MUTAGEN SOCIETY OF INDIA

47th Annual Meeting & Golden Jubilee Year of the Environmental Mutagen Society of India
International Conference on Environmental and Molecular Mutagenesis: Genomic Integrity and Implications to Human Health (EMSI-2025)
January 29 – 31, 2025

CERTIFICATE

This is to certify that Ms. Rashmi RN participated in the "International Conference on Environmental and Molecular Mutagenesis: Genomic Integrity and Implications to Human Health (EMSI-2025)" during January 29-31, 2025 at the Department of Biochemistry and Biotechnology, Annamalai University. She has delivered a Poster Presentation entitled Maternal Folate Status and its Association of MTHFR Gene Expression in Pre-Eclampsia.

Dr. N. Rajendra Prasad, Convener, EMSI-2025 | Dr. S. Manoharan, Chairperson, EMSI-2025 | Dr. S. Sriram, Dean, Faculty of Science, Annamalai University | Dr. Bani Bandana Ganguly, President, EMSI | Prof. M. Prakash, Registrar (i/c), Annamalai University

ICCD 2025

St. Peter's Medical College, Hospital & Research Institute
Dr. MGR Nagar, Opp. SIPCOT I, Hosur, Tamilnadu - 635109

ST. PETER'S

ICCD 2025 - ORAL PRESENTATION

International Confluence of Clinicians & Diagnosticians - 2025

This certificate is proudly presented to

RASHMI RN

for Oral presentation titled **Maternal Folate Status and Placental Neuro-Vascular Changes in Early-Onset Versus Late-Onset Preeclampsia** in **International Confluence of Clinicians & Diagnosticians** held on 29th & 30th of November 2025. Organised by Department of Biochemistry in association with Department of General Medicine, SPMCH & RI, Hosur.

Scientific Chairperson, Dr. Shankar Kanumakala | President, Dr. Vinoth. S | Organising Secretary, Dr. Deepak Anand. R | Organising Secretary, Dr. Thivyaprabha. AG
Vice Principal, Dr. Anand Reddy | Medical Superintendent, Dr. Girish F Hongal | Dean, Dr. Rajamuthaiah

SZACBICON - 2025

THE SOUTH ZONE ACBI CONFERENCE

Organized by: Departments of Biochemistry, JIPMER & IGMC&RI, Puducherry
Theme: Translation from the bench to the bedside:Emerging trends in clinical biochemistry to improve patient outcomes
Venue: JIPMER, Puducherry | Date: 24th - 25th January 2025

Certificate of Participation

This is to certify that

Rashmi RN

has participated as a delegate and presented **e-POSTER** titled "***Maternal Folate Levels and MTHFR Gene Influence on Preeclampsia Severity: Implications for Pregnancy Management***" in a Scientific Session at the South Zone Conference of Association of Clinical Biochemists of India (SZACBICON)-2025 held on 24th- 25th January 2025 at JIPMER, Puducherry.

Dr. Zechariah Bobby, Organizing Chairman | Dr. R. Ramesh, HOD of Biochemistry, JIPMER | Dr Medha Rajappa, Organizing Secretary | Dr. R. Vinayagamoorthi, Joint Organizing Secretary